Remarks

Claim 26 is amended.

Claim Rejections 35 USC § 112

Applicants have deleted the term "less often." Thus, Applicants believe that the claims now satisfy the requirements of § 112.

Claim Rejections- 35 USC § 103

1. NO PRIMA FACIE CASE OF OBVIOUSNESS EXISTS BECAUSE BANDYOPADHYAY IS NOT PRIOR ART.

The claims were rejected "as being unpatentable over Larsson (Arch Ophthalmol., Vol. 119, 2001, pp. 492-495) in view of Bandyopadhyay (US 2002/0128267). The *prima facie* case relies upon the combination of these references. "[A]n obviousness rejection based on a publication which would be applied under 102(a) if it anticipated the claims can be overcome by swearing behind the publication date of the reference by filing an affidavit or declaration under 37 CFR 1.131." Applicants enclose herewith a rule 131 affidavit filed in the parent case that establishes that the presently claimed invention was made by April 19, 2001. Since Bandyopadhyaya was filed on May 4, 2001, it is not prior art. Thus, no prima facie case of obviousness has been made.

2. NO *PRIMA FACIE* CASE OF OBVIOUSNESS EXISTS BECAUSE IT RESTS UPON THE FAULTY PRESUMPTION THAT ALL METHODS OF ADMINISTERING A COMBINATION OF TIMOLOL AND BRIMONIDINE ARE EQUAL.

Any prima facie case of obviousness would rely upon the position that Larsson's teaching of sequential administration of 0.5% timolol topically followed by administration of 0.2% brimonidine five minutes later, suggests combination of the two drugs into a single composition. In order for the Office to make a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP 2143. If Larsson does suggest that the regime that it teaches might be altered, there are a potentially infinite number of ways that the administration schedule of Larsson might be modified. Thus, the group of potential modifications to Larsson's dosing regime is a genus itself. "The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." MPEP 2144.08 II citing *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). It follows that the fact that a particular reference suggests a genus "is not sufficient by itself to establish a *prima facie* case of obviousness."

Enclosed herewith is a Rule 132 affidavit filed in a related case showing that the order of administration of timolol and brimonine to the eye of rabbits has a significant effect upon the C_{max} and AUC of timolol. In this particular study, where all other factors

were equal except order of administration, significantly higher C_{max} and AUC for timolol in the aqueous humor were observed when brimonidine was administered first (C_{max} = 3.18 μg/mL; AUC = 260 μg·min/mL) as compared to when timolol was administered first (C_{max} = 1.57 μg/mL; AUC = 174 μg·min/mL). For the adjunctive treatments, the two drops were administered ten minutes apart. Similarly, significantly higher C_{max} and AUC for timolol in the aqueous humor were observed when brimonidine was administered first as compared to when a single composition containing both drugs was administered (C_{max} = 1.24 μg/mL; AUC = 171 μg·min/mL). (See summary, p. 4, Exhibit A).

These results demonstrate that administration of the two drugs is a genus of at least four distinct species in light of Larrson: 1) administration of 0.2% brimonidine, wait 10 minutes, administration of 0.5% timolol; 2) administration of 0.2% brimonidine, wait 5 minutes, administration of 0.5% timolol; 3) administration of 0.5% timolol, wait 10 minutes, administration of 0.2% brimonidine; and 4) administration of a single composition containing 0.2% brimonidine and 0.2% timolol. Furthermore, since administration of brimonidine 10 minutes before administration of timolol has a significantly different effect than administering the two at the same time (i.e. time = 0), one can conclude that the pharmacokinetics are dependent upon the time between administration of the two drugs. Thus, there are literally an infinite amount of dosage regimes between the Larsson regimen and administration of the claimed compound, and the genus comprising both is literally infinite. Therefore, the assertion by the Office that Larsson suggests this genus "is not sufficient by itself to establish a *prima facie* case of obviousness."

3. ALTERNATIVELY, THE FACT THAT THE ORDER OF ADMINISTRATION OF THE DRUGS AFFECTS THE PHARMACOKINETIC PROFILE IS UNEXPECTED.

If a *prima facie* case of obviousness were established, then the presently presented pharmacokinetic results are necessarily unexpected. Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness. MPEP 2144.08 (b)(6) As explained above, a *prima facie* case of obviousness in the present case depends upon the assumption that all methods of topically administering a combination of 0.2% brimonidine and 0.5% timolol to a person are equivalent. If all these methods of administration are equivalent, a person of ordinary skill in the art would not expect to see any differences between them. Thus, the fact that administration of 0.2% brimonidine before 0.5% timolol in rabbits results in about twice the concentration of timolol in the aqueous humor as compared to administration 0.2% brimonidine and 0.5% timolol in a single composition is unexpected. Thus, if one accepts that a *prima facie* case of obviousness has been made, he should also accept that the results presented herein are unexpected and that said *prima facie* case is overcome.

In light of the affidavit submitted herewith and the arguments made herein, Applicants believe that the claims are patentable as they stand. Therefore, Examiner is respectfully requested to allow the claims.

Please charge Deposit Account 01-0885 for any fees related to this response.

Respectfully submitted,

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Rule 131 affidavit
Rule 132 affidavit